REMARKS

Applicants thank the Office for the attention accorded the present Application in the June 29, 2005, Office Action. In that Action, Claims 5 and 7 were objected to for misspelled words, and Claims 1-14 were rejected under 35 USC §103(a) as being unpatentable over Powell et al.(US 6,140,319).

Applicants have amended Claim 5 to include the correct spelling of the word "propranolol." Applicants have also amended Claim 7 to include the correct spelling of the word "metoprolol." In light of Applicants' amendments, Applicants respectfully request that the Office withdrawn its claim objections.

35 USC §103(a) rejection:

The Office has rejected Claims 1-14 under 35 USC §103(a) as being unpatentable over Powell et al. The Office states that Powell et al. teach a single dosage unit of a vasopeptidase inhibitor combined with a beta-blocker and an antiplatelet agent where the difference is the inclusion of a vasopeptidase inhibitor. The Office further states that absent a clear indication in the specification or claims of the basic and novel characteristics of the present invention, the transition phrase "consisting essentially of" will be construed as equivalent to "comprising" and that the Applicants have the burden of showing that the introduction of additional steps or components would materially change the characteristics of Applicants' invention.

Applicants respectfully traverse.

Applicants object to the Office's arbitrary interpretation of the transition phrase

"consisting essentially of" as equivalent to "comprising" as being contrary to established law. "Consisting essentially of" is a transition phrase that occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format. "Consisting essentially of" opens a claim to unlisted ingredients that do not materially affect the basic and novel properties of the invention. It is not equivalent to a "comprising" format.

Contrary to the Office's assertion, the addition of a vasopeptidase inhibitor would substantially change the characteristics of the present invention.

Vasopeptidase inhibitor and omapatrilat, as taught by Powell et al., in combination with a beta-adrenergic blocking agent would result in a dosage unit that inherently has added risk for an individual with cardiovascular disease. The use of vasopeptidase inhibitors increases the risk of angioedema. Angioedema is characterized by swelling of the tissues such as the skin and the gastrointestinal and respiratory tracts. Involvement of the airway with swelling causing closure can be life threatening. Angioedema relates to allergic conditions in which the adrenergic pathways are impaired. Treatments include adrenergic stimulatory agents such as epinepherine. In fact, the ACE inhibitor Zestril (See PDR 2001, page 656; attached as Exhibit 1) carries the warning ". . . angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. subcutaneous epinepherine solution 1:1000 (0.30 ml to 0.5 ml) and/or measures necessary to ensure a patient airway should be promptly provided."

Other studies have ascertained this added risk. Experience with the vasopeptidase inhibitor, omapatrilat, is reported by A. Coates in Omapatrilat – the story of Overture and Octave, International Journal of Cardiology, November 2002, 86(1):1. (See Exhibit 2). Significantly more cases of angioedema were seen with Omapatrilat than with enalapril. Overall death rates were similar and all adverse events were similar. The rates of angioedema were much higher in blacks and for smokers. In summary, Coates states that "we were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison."

In another study, a clinical perspective and reassessment of the mechanisms for angioedema caused by other inhibitors of the renin-angiotensin system was considered by A.G. Chiu, E.J. Krowiak and Z.E. Deeb in Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology, Laryngoscope, October 2001, 111(10), 1729-1731. (See Exhibit 3). The authors review the literature and report three cases of AT2 receptor antagonist-induced angioedema, one which required surgical airway intervention. The authors state that angioedema is a potentially life-threatening condition commonly associated with ACE inhibitor use. They further state that the incidence of AT2 blocker-induced angioedema brings into question prior theories on the etiology of angioedema and its pathogenesis.

Applicants further point out the potential for vasopeptidase inhibitor-induced angioedema is worsened by the combination of a vasopeptidase inhibitor with a beta-

adrenergic blocking agent. The concomitant use of adrenergic blocking agents with vasopeptidase inhibitors increases the potential for angioedema to occur and the likelihood for more severe and intractable angioedema, and decreases the efficacy of rescue treatments with adrenergic stimulatory agents. The beta-blocker Ternomin (PDR 2001, page 650; attached as Exhibit 4) discloses the precaution that "while taking beta blockers, patients with a history of anaphylactic reaction may have a more severe reaction and such patients may be unresponsive to the usual doses of epinepherine used to treat the allergic reaction." The beta-blocker Indereal (PDR 2001, page 3379; attached as Exhibit 5) carries a similar warning.

The results of aspirin therapy are well known and documented in Applicants' specification. The results of beta-blocker therapy are likewise documented and further reflected in Applicants' previous literature submissions. Applicants assert that these protective results clearly contrast those that would be anticipated from treating individuals with cardiovascular disease with a combination that would place them at risk from serious side effects requiring cardiac-stimulatory medications such as epinepherine to reverse such side effects. **Such a combination would be the antithesis of protective.** In view of this contradiction, Powell et al. teach the addition of an ingredient that materially affects the basic and novel characteristics of Applicants' invention.

Powell et al. fail to disclose a combination of anti-adrenergic and anti-platelet agents without a vasopeptidase inhibitor. The use of vasopeptidase inhibitors increases the risk for a more severe and intractable angioedema for which the usual

doses of an andrenergic stimulatory agent may be insufficient because of the combination of the vasopeptidase inhibitor with an anti-adrenergic agent.

Unlike the addition of incipients such as binders and stabilizers that have no effect on the characteristics of Applicants' invention, it is clear that the increased risks associated with vasopeptidase inhibitors render the addition of vasopeptidase inhibitors in Applicants' invention as materially affecting the basic characteristics of Applicants' claimed invention.

In light of Applicants' amendments and the arguments presented, Applicants respectfully submit that the 35 USC §103(a) rejection of Claims 1-14 has been successfully traversed. Allowance is therefore requested.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 9/12/05

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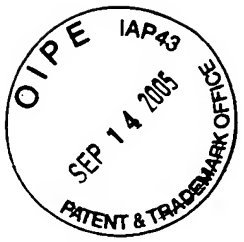

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September 12, 2005
Robert R. Deleault

Exhibit 7

Zestril—Cont.

single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.

The antihypertensive effects of ZESTRIL are maintained during long-term therapy. Abrupt withdrawal of ZESTRIL has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilizing a once daily regimen were conducted in 438 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of ZESTRIL was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 40 mg of ZESTRIL. In controlled clinical studies, ZESTRIL 20–80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5–50 mg and with atenolol 50–200 mg; and in patients with moderate to severe hypertension to metoprolol 100–200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 3/4 Caucasian. ZESTRIL was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

ZESTRIL had similar effectiveness and adverse effects in younger and older (> 65 years) patients. It was less effective in blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of ZESTRIL, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension ZESTRIL has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

Heart Failure: During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single doses of ZESTRIL resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

In two placebo controlled, 12-week clinical studies, using doses of ZESTRIL up to 20 mg, ZESTRIL as adjunctive therapy to digitalis and diuretics improved the following signs and symptoms due to congestive heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies, beneficial response was also noted for: orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in this study. The once daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic response. A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

Acute Myocardial Infarction: The Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on longer-term death and markedly impaired cardiac function. Patients presenting within 24 hours of the onset of symptoms who were hemodynamically stable were randomized, in a 2 × 2 factorial design, to six weeks of either 1) ZESTRIL alone (n=4841), 2) nitrates alone (n=4869), 3) ZESTRIL plus nitrates (n=4841), or 4) open control (n=4843). All patients received routine therapies, including thrombolytics (72%), aspirin (64%), and a beta-blocker (31%), as appropriate, normally utilized in acute myocardial infarction (MI) patients. The protocol excluded patients with hypotension (systolic blood pressure ≤ 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine >2 mg/dL and/or proteinuria > 500 mg/24 h). Doses of ZESTRIL were adjusted as necessary according to protocol (see DOSAGE AND ADMINISTRATION).

Study treatment was withdrawn at six weeks except where Patients receiving ZESTRIL (n=9646), alone or with nitrates, had an 11% lower risk of death (2p [two-tailed] = 0.04) compared to patients receiving no ZESTRIL (n=9672) (6.4% vs. 7.2%, respectively) at six weeks. Although patients randomized to receive ZESTRIL for up to six weeks also fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with ZESTRIL, had a higher (9.0% versus 9.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hour) and renal dysfunction (2.4% versus 1.1%) in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). See ADVERSE REACTIONS—Acute Myocardial Infarction.

INDICATIONS AND USAGE

Hypertension: ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

Heart Failure: ZESTRIL is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

Acute Myocardial Infarction: ZESTRIL is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.)

In considering the use of ZESTRIL, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks. In addition, ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Angioedema).

CONTRAINDICATIONS

ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ZESTRIL) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. ZESTRIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihyper-

Patients with heart failure given ZESTRI
some reduction in blood pressure, with pe
reduction occurring 6 to 8 hours post do
the two-dose ATLAS trial suggested that
tension may increase with dose of lisinop
patients. Discontinuation of therapy bec
symptomatic hypotension usually is no
dosing instructions are followed; caution
when initiating therapy. (See DOSAGE
TRATION.)

Patients at risk of excessive hypotension
ated with oliguria and/or progressive az
with acute renal failure and/or death, inc
following conditions or characteristics:
systolic blood pressure below 100 mm
high dose diuretic therapy, recent inter
crease in diuretic dose, renal dialysis
and/or salt depletion of any etiology. It
eliminate the diuretic (except in patie
ure), reduce the diuretic dose or increa
tiously before initiating therapy with Z
at risk for excessive hypotension who
such adjustments. (See PRECAUTION
and ADVERSE REACTIONS.)

Patients with acute myocardial infarc
trial had a higher (9.0% versus 9.7%) in
hypotension (systolic blood pressure <
than 1 hour) when treated with ZEST
ZESTRIL must not be initiated in acu
tion patients at risk of further serious
oration after treatment with a vaso
blood pressure at 100 mmHg or lower)

In patients at risk of excessive hypote
be started under very close medical
patients should be followed closely for
treatment and whenever the dose of
uretic is increased. Similar considerat
tients with ischemic heart or cerebrov
patients with acute myocardial infar
cessive fall in blood pressure could r
infarction or cerebrovascular accident

If excessive hypotension occurs, th
placed in the supine position and, if
intravenous infusion of normal saline
sive response is not a contraindicati
ZESTRIL which usually can be given
the blood pressure has stabilized. If
sion develops, a dose reduction
ZESTRIL or concomitant diuretic ma

Leukopenia/Neutropenia/Agranulo
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shown to cause agranulocytosis and
sion, rarely in uncomplicated patien
in patients with renal impairment
have a collagen vascular disease. Av
cal trials of ZESTRIL are insufficient
does not cause agranulocytosis at si
experience has revealed rare cases
nia and bone marrow depression in
ship to lisinopril cannot be excluded
white blood cell counts in patients
disease and renal disease should be

Hepatic Failure: Rarely, ACE inhil
ated with a syndrome that starts w
and progresses to fulminant hepa
times) death. The mechanism of thi
stood. Patients receiving ACE inhil
dice or marked elevations of hepati
tinue the ACE inhibitor and rece
follow-up.

Fetal/Neonatal Morbidity and Mo
can cause fetal and neonatal morbi
ministered to pregnant women. S
been reported in the world literat
detected, ACE inhibitors should be
possible.

The use of ACE inhibitors during
mesters of pregnancy has been a
neonatal injury, including hypoten
plasia, anuria, reversible or irrev
death. Oligohydramnios has also b
resulting from decreased fetal ren
nics in this setting has been assoc
tractures, craniofacial deformati
development. Prematurity, intrau
and patent ductus arteriosus hav
though it is not clear whether thes
the ACE-inhibitor exposure.

These adverse effects do not app
intrauterine ACE-inhibitor expos
to the first trimester. Mothers w
are exposed to ACE inhibitors on
ter should be so informed. None
come pregnant, physicians shoul
continue the use of ZESTRIL as
Rarely (probably less often tha
pregnancies), no alternative to AC
In these rare cases, the mothers

Exhibit 2

1: Int J Cardiol 2002 Nov;86(1):1

Omapatrilat- the story of Overture and Octave.

Coats A.

Viscount Royston Professor of Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, at Royal Brompton Hospital, Sydney St., SW3 6NP, London, UK

At the American College of Cardiology in March two major trials were presented. The publicity surrounding the two could not have been more different. The LIFE demonstrated clear superiority of losartan-based therapy over atenolol-based therapy for the treatment of hypertension. It was published the same week in the Lancet and received major press coverage all over the world.The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study in contrast received a subdued reception, very little publicity and is yet to be published. 5770 NYHA class II-IV heart failure patients (LVEF</=30%, recent heart failure hospital admission) were randomised and uptitrated to either 10 mg BD of Enalapril or 40 mg once a day Omapatrilat. The primary end-point of all cause mortality or heart failure related hospitalisation did not differ significantly: 914/2884 for Enalapril and 914/2886 for Omapatrilat (hazard ratio 0.94, CI's 0.86-1.03, P=0.187). Mortality was also similar: 509 for Enalapril and 477 for Omapatrilat (hazard ratio 0.94, CI's 0.83-1.07, P=0.339). Omapatrilat was as good as Enalapril but not better. The worrying trend was however, that angioedema was more common with Omapatrilat; 24 (0.8%) versus 14 cases (0.5%).The OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study was also presented at this time. 25,267 hypertensives were randomised to Omapatrilat or enalapril and a difference of approximately 3 mmHg in favour of Omapatrilat was seen. Significantly more cases of angioedema were seen with Omapatrilat, 274 (2.17%) compared to 86 (0.68%) with enalapril. Overall death rates were similar, 0.18% for enalapril and 0.15% for Omapatrilat. All adverse events were similar, 51.0% for Omapatrilat and 50.4% for enalapril. The rates of angioedema were much higher in blacks, 5.54% for Ompatrilat and 1.62% for enalapril and for smokers, 3.93% for Omapatrilat and 0.81% for enalapril. We were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison. The medical community will be watching to make sure these data are published in full in the medical literature in a timely fashion, in the order of end-points specified in the protocol and with appropriate emphasis on the logical points of presentation.

PMID: 12243845 [PubMed - in process]

Exhibit 3

1: Laryngoscope 2001 Oct;111(10):1729-31

Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology.

Chiu AG, Krowiak EJ, Deeb ZE.

Department of Otolaryngology--Head and Neck Surgery, The Washington Hospital Center and Georgetown University Medical Center, Washington DC, USA. Alexchiu11@hotmail.com

INTRODUCTION: Use of angiotensin converting enzyme inhibitors has long been associated with angioedema. Increased levels of bradykinin caused by the inhibition of angiotensin converting enzyme have been thought to be responsible for this side effect. Angiotensin II receptor antagonists (AT2 blockers), such as losartan potassium (Cozaar; Merck & Co., West Point, PA), are a new class of antihypertensives developed in part to eliminate cough and angioedema associated with ACE inhibitors. These agents act by selectively binding to angiotensin II receptor sites, thereby eliminating the hypertensive effects of angiotensin without affecting local and systemic bradykinin levels. We present three cases of AT2 receptor antagonist-induced angioedema, and examine its significance in the treatment of angioedema and its proposed etiology. METHODS: A retrospective chart review and review of the literature. RESULTS: Three patients taking the AT2 blocker losartan presented with mucosal swelling in the head and neck clinically consistent with angioedema. All three patients had prior episodes of angioedema while on losartan. Two patients presented with involvement of the anterior tongue and face that resolved within 12 hours of discontinuation of the losartan and a course of intravenous steroids. The third patient experienced recurring episodes of angioedema that eventually required a tracheotomy for airway compromise. After discontinuing the losartan and receiving a course of intravenous steroids, the angioedema resolved in 5 days. The patient was decannulated 10 days after onset of symptoms. CONCLUSION: Angioedema is a potentially life-threatening condition commonly associated with ACE inhibitor use. AT2 blockers bind to angiotensin II receptor sites and have no demonstrable effect on local or systemic bradykinin levels. We present three cases that demonstrate AT2 blocker-induced angioedema. They were all complicated by the fact that the inciting agent, losartan, was not discontinued after the initial episode and resulted in recurrent episodes of angioedema, one of which required surgical airway intervention. The incidence of AT2 blocker-induced angioedema brings into question prior theories on the etiology of angioedema and bradykinin's role in its pathogenesis.

PMID: 11801934 [PubMed - indexed for MEDLINE]

Exhibit 4

stimulation is necessary in
in congestive heart failure,
tential hazard of further de-
y and precipitating more se-
ve congestive heart failure
uretics, TENORMIN should
digitalis and atenolol slow

al infarction, cardiac failure
ively controlled by 80 mg of
alent therapy is a contrain-
nt.

f Cardiac Failure: Contin-
rdium with beta-blocking
, in some cases, lead to car-
symptom of impending car-
treated appropriately ac-
led guidelines, and the re-
ac failure continues despite
IN should be withdrawn.
RATION.)

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advised against abrupt
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e been reported in an-
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TENORMIN is planned,
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minimum. If the angina
fficiency develops, it is
IN be promptly reinsti-
ecause coronary artery
be unrecognized, it may
e TENORMIN therapy
ated only for hyperten-
MINISTRATION.)

nnel Blockers: Bradycar-
nd the left ventricular end
beta blockers are adminis-
n. Patients with pre-exist-
eft ventricular dysfunction
PRECAUTIONS.)

**ENTS WITH BRONCHO-
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itantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

Untreated Pheochromocytoma: TENORMIN and TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

Pregnancy and Fetal Injury: Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose*. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose*.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

PRECAUTIONS

General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium channel blockers may also have an additive effect when given with TENORMIN (See WARNINGS.).

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Usage in Pregnancy: **Pregnancy Category D:** See WARNINGS—Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

[See table at left]

Volunteered (US Studies)		Total—Volunteered and Elicited (Foreign + US Studies)	
Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
3	0	3	0
0	0.5	12	5
2	1	4	5
0	0.5	3	1
4	1	13	6
2	0.5	2	0.2
1	0	3	0.7
0.6	0.5	26	13
3	1	6	5
1	0	3	0.7
0.8	0	2	0.5
0.6	0.5	12	9
0	0	3	1

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Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

[See first table at top of next page]

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either

hypotension which may be asso
rash or exacerbation of p
reversible alopecia, thr
disturbances, sick sinus synd
ENORMIN, like other beta block
the development of antinucle
syndrome, and Raynaud's phe

POTENTIAL ADVERSE EFFEC
In addition, a variety of adverse e
with other beta-adrenergic blockin
sidered potential adverse effects o
Hematologic: Agranulocytosis.
Allergic: Fever, combined with a
ryngospasm, and respiratory dist
Central Nervous System: Reve
progressing to catatonia; an ac
characterized by disorientation
term memory loss; emotional lab
sensorium; and decreased perform
rics.
Gastrointestinal: Mesenteric art
colitis.
Other: Erythematous rash.
Miscellaneous: There have be
and/ or dry eyes associated with
blocking drugs. The reported inci
cases, the symptoms have clea
withdrawn. Discontinuance of t
ered if any such reaction is no
tients should be closely monito
therapy. (SEE DOSAGE AND A
The oculomucocutaneous syndro
blocker practolol has not been
Furthermore, a number of pa
demonstrated established prac
ferred to TENORMIN therapy
or quiescence of the reaction.

OVERDOSAGE
Overdosage with TENORMIN
tients surviving acute doses as
reported in a man who may h
acutely.
The predominant sympt
TENORMIN overdose are leth
drive, wheezing, sinus pause a
common effects associated wi
adrenergic blocking agent and
in TENORMIN overdose are c
tension, bronchospasm and/or
Treatment of overdose should
any unabsorbed drug by induc
administration of activated c
removed from the general c
Other treatment modalities sh
sician's discretion and may in
BRADYCARDIA: Atropine int
sponse to vagal blockade, giv
refractory cases, a transvenou
indicated.
HEART BLOCK (SECOND C
terenol or transvenous cardia
CARDIAC FAILURE: Digitali
a diuretic. Glucagon has bee
HYPOTENSION: Vasopress
epinephrine (levarterenol).
tinuously.
BRONCHOSPASM: A $beta_2$ a
or terbutaline and/or aminop
HYPOGLYCEMIA: Intraven
Based on the severity of sy
quire intensive support care
diac and respiratory support

DOSAGE AND ADMINIST
Hypertension: The initial
given as one tablet a day ei
therapy. The full effect of
within one to two weeks.
achieved, the dosage shoul
100 mg given as one tablet
yond 100 mg a day is unlike
fit.
TENORMIN may be used al
antihypertensive agents in
hydralazine, prazosin, and
Angina Pectoris: The initi
given as one tablet a day.
achieved within one week, t
TENORMIN 100 mg given
tients may require a dosage
effect.
Twenty-four hour control w
by giving doses larger tha
mate maximum effect. Th
tolerance occurs with d
doses the effect at 24 hour
50% to 75% of that observ

Exh 16-5

general anesthesia and surgical procedures.

Inderal, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

Diabetes and Hypoglycemia

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occurred in renal insufficiency, both during dialysis and sporadically, in subjects on propranolol.

Thyrotoxicosis

Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3 and decreasing T_3.

In Patients With Wolff-Parkinson-White Syndrome, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General

Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderal may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Risk of anaphylactic reaction. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Clinical Laboratory Tests

Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Drug Interactions

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if Inderal is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. In a study in which both male and female rats were exposed to propranolol in their diets at studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day (> 10 times the maximum recommended human daily dose of propranolol on a body weight basis), but not at doses of 80 mg/kg/day, treatment was associated with embryotoxicity (reduced litter size and increased resorption sites) as well as neonatal toxicity (deaths). Propranolol also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (> 15 times the maximum recommended daily human dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and respiratory depression. Adequate facilities for monitoring these infants at birth should be available. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

Pediatric Use

High serum propranolol levels have been noted in patients with Down's syndrome (trisomy 21), suggesting that the bioavailability of propranolol may be increased in patients with this condition.

Evaluation of the effects of propranolol in pediatric patients, relative to the drug's efficacy and safety, has not been as systematically performed as in adults. Information is available in the medical literature to allow fair estimates, and specific dosing information has been reasonably studied.

Cardiovascular diseases that are common to adults and children are generally as responsive to propranolol intervention in children as they are in adults.

Adverse reactions are also similar: for example, bronchospasm and congestive heart failure related to propranolol therapy have been reported in pediatric patients and occur through the same mechanisms as previously described in adults.

The normal echocardiogram evolves through a series of changes as the heart matures during growth and development in pediatric patients. Should echocardiography be used to monitor propranolol therapy in pediatric patients, the age-related changes in the echocardiogram need to be borne in mind.

Geriatric Use

Clinical studies of propranolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations, vivid dreams, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. Total daily doses above 160 mg (when administered as divided doses of greater than 80 mg each) may be associated with an increased incidence of fatigue, lethargy, and vivid dreams.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivas reported for a beta blocker (practolol) have not been associated with propranolol.

achieved. The usual maintenance
mg per day. In some instances
be required. The time needed
sponse to a given dosage is
few days to several weeks.
While twice-daily dosing is
duction in blood pressure
tients, especially when low
ence a modest rise in blood
12-hour dosing interval. Th
ing blood pressure near the
termine whether satisfacto
throughout the day. If contr
or 3-times-daily therapy ma
Angina Pectoris—*Dosage m*
Total daily doses of 80 mg
orally, twice a day, three ti
have been shown to increas
duce ischemic changes in th
continued, reduce dosage gr
weeks. (See "WARNINGS."
Arrhythmias—10 mg to 30 m
fore meals and at bedtime.
Myocardial Infarction—The
180 mg to 240 mg per day in
regimen was used in the B
and a q.i.d. regimen in the
there is a reasonable basis
b.i.d. regimen (see "CLINIC
effectiveness and safety of
mg for prevention of cardiac
lished. However, higher do
tively treat coexisting diseas
sion (see above).
Migraine—*Dosage must be i*
The initial oral dose is 80 mg
The usual effective dose ran
The dosage may be increased
migraine prophylaxis. If a s
tained within four to six wee
dose, Inderal therapy should
visable to withdraw the drug
eral weeks.
Essential Tremor—*Dosage m*
The initial dosage is 40 mg
reduction of essential tremor
of 120 mg per day. Occasiona
minister 240 mg to 320 mg p
Hypertrophic Subaortic Sten
four times daily, before meal
Pheochromocytoma—*Preop*
vided doses for three days p
with an alpha-adrenergic blo
—*Management of inoperable*
doses.
Use in Pediatric Patients:
Inderal is not recommended
age for treating hypertensio
beginning with a 1.0 mg per
age regimen (i.e., 0.5 mg per
The usual pediatric dosage ra
day in two equally divided do
2.0 mg per kg b.i.d.). Pediatr
(recommended) generally pro
els in a therapeutic range sin
other hand, pediatric doses c
surface area (not recommen
levels above the mean adult t
16 mg per kg per day shoul
tients. If treatment with In
gradually decreasing dose ti
riod is necessary.
Intravenous
Parenteral drug products sh
particulate matter and disc
tion, whenever solution and
Intravenous administration i
arrhythmias or those occurrin
dose is from 1 mg to 3 mg ad
itoring, e.g., electrocardiogra
The rate of administration sl
per minute to diminish the
pressure and causing cardi
should be allowed for the dr
even when a slow circulation
ond dose may be given after t
tional drug should not be give
ditional Inderal should not be
ation in rate and/or rhythm h
Transference to oral therapy s
sible.

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